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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,443	07/30/2001	Lars Christian Ronn	P66506US0	6998

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,443	RONN ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *98-147* is/are pending in the application.

4a) Of the above claim(s) *114-122 and 126-134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *98-113 and 135-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *98-147* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment filed 15 September 2003 has been received and entered in *part*. Claims 56-97 have been cancelled and claims 98-147 have been added.

2. Newly submitted claims **114-122** and **126-134** are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: said claims encompass therapies and nerve prosthetics not included in the original election.

3. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims **114-122** and **126-134** are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Claims **98-113** and **135-147** are currently under examination.

Election/Restriction

5. The Applicant continues to traverse the restriction requirement set forth in Restriction Requirement (14 March 2003) on the following grounds: the USPTO should acknowledge and honor the finding regarding unity of invention made by the Swedish Patent Office in connection with the PCT prosecution of the instant application.

6. The Examiner has taken the Applicant's argument into consideration and is not found persuasive. The Examiner respectfully submits that the USPTO is not bound by decisions made by foreign patent offices and authorities concerning foreign applications. Once PCT/DK99/00500 was filed under 35 U.S.C. §371(c) it is in the domain of the USPTO. All

decisions are made pursuant to the relevant United States Code or sections of the PCT (MPEP §1875 and §1893.03). In the instant case, it is the policy of the USPTO to use Unity of Invention (PCT Rule 13) practice in lieu of 35 U.S.C. §121 for restriction/election requirements on applications filed under 35 U.S.C. §371 [see 37 C.F.R. 1.475, MPEP §1893, and *Caterpillar Tractor Co. v. Commissioner of Patents and Trademarks*, 231 USPQ 590 (E.D. Va. 1986)]. Therefore, the Requirement for Restriction was made under the Lack of Unity requirement pursuant to the PCT Rule 13 (Restriction Requirement 14 March 2003). Finally, Applicant is entitled to petition all restriction requirements made by the USPTO, whether under 35 U.S.C. §121 or the Lack of Unity rule PCT Rule 13, pursuant to 37 C.F.R. 1.181. The Restriction Requirement in question was made FINAL in the Non-Final Rejection mailed 15 April 2003.

Specification

7. The disclosure is objected to because of the following informalities: the Amendment filed 15 September 2003 does not incorporate any changes to the Specification as filed. Thus said Amendments have not been entered.

Withdrawn Objections And/Or Rejections

8. The Objection to the Drawings as set for at pp. 3 ¶5 in the previous Office Action (15 April 2003) is hereby *withdrawn* in view of proposed drawing corrections (15 September 2003).

9. The Objection to the Oath/Declaration as set for at pp. 4 ¶8 in the previous Office Action (15 April 2003) is hereby *withdrawn* in view replacement Oath/Declaration (15 September 2003).

10. The Objection to the Specification as set for at pp. 4 ¶9 in the previous Office Action (15 April 2003) is hereby *withdrawn* in view of amendments (15 September 2003).

11. The Objection to claims 56, 60, and 61 as set for at pp. 4 ¶10 in the previous Office Action (15 April 2003) is *moot* in view cancellation of said claims (15 September 2003).

12. The Rejection of claims 56 and 60 under 35 U.S.C. §112 ¶2 as set for at pp. 10-11 ¶25-27 in the previous Office Action (15 April 2003) is *moot* in view cancellation of said claims (15 September 2003).

Maintained Objections And/Or Rejections

13. The Objection to the Specification under "Sequence Rules" as set for at pp. 3 ¶6-7 in the previous Office Action (15 April 2003) is *maintained* due to errors contained in the CRF filed on 15 September 2003. Applicant is invited to review the error report included herein and resubmit the CRF.

14. Claims **98-113** and **135-147** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *polypeptides having an amino acid sequence of at most 12 amino acid residues from the amino acid sequence of neural cell adhesion molecule (NCAM) wherein said polypeptide is selected from the group consisting of ASKKPKRNIKA (SEQ IN NO: 1), AKKERQRKDTQ (SEQ IN NO: 2), ARALNWGAKPK (SEQ IN NO: 3), AGSAVKLKKKA (SEQ IN NO: 4), ATNKKTGRRRR (SEQ IN NO: 9), ARQKTMKPRRS (SEQ IN NO: 12), ARKTRERKSKD (SEQ IN NO: 14), ASQAKRRRKGPR (SEQ IN NO: 15), AKKEKPNKPND (SEQ IN NO: 17), AEGGKKKKMRA (SEQ IN NO: 19), AKKKEQKQRNA*

(SEQ IN NO: 20), AKSRKGNSSLM (SEQ IN NO: 21), and ARKSRDMTAIK (SEQ IN NO: 22) and wherein said polypeptide binds NCAM Ig1-Ig2 domains and stimulates or promotes neurite outgrowth from NCAM presenting cells and/or proliferating thereof, does not reasonably provide enablement for *a mimic thereof having an amino acid sequence of at most 12 amino acid residues, wherein said amino acid sequence of the compound comprises the sequence K/R0-1-K/R-X-K/R, wherein X is any amino acid.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims for the reasons set forth at pp. 10-11 ¶25-27 in the previous Office Action (15 April 2003).

15. The Applicant traverses the rejection set forth in the previous Office Action for claims 56-66 and 70-73 herein applied to newly added claims 98-113 and 135-147 on the following grounds: **(a)** the Specification as written contains a concise written description of the invention and exhaustively supplemented with a description of examples of how to make and use the same, **(b)** the claims as currently presented are drawn to a specific genus of compounds with a specific function and not just any fragment of NCAM, **(c)** the Specification includes SEQ ID NO: 1, 2, 3 with examples of their activity including Table 7 providing guidance for making similar homologues, **(d)** the Specification contains detailed guidance concerning the importance of basic amino acid residues in the motif "K/R_{0-1}-K/R-X-K/R", **(e)** the Specification provides a number of examples enabling a skilled artisan to practice the invention, **(f)** Frei *et al.* (1992) is not relevant to enablement of the present invention, **(g)** the NCAM isoforms as taught by Doherty *et al.* (March 1995) "The Neural Cell Adhesion Molecule and Synaptic Plasticity." J. Neurobiol. **26**(3): 437-446 cannot be considered "mimics" in view of the limitations of the instant claims,

(h) Rao *et al.* (August 1992) "Identification of a Peptide Sequence Involved in Homophilic Binding in the Neural Cell Adhesion Molecule (NCAM)" The Journal of Cell Biology **118**(4): 937-949 (**IDS #DE**) and Rao *et al.* (4 November 1994) "Mechanism of Homophilic Binding Mediated by the Neural Cell Adhesion Molecule NCAM." The Journal of Biological Chemistry **269**(44): 27540-27548 (**IDS #DF**) do not discuss the motif currently claimed ("K/R_{0-1}-K/R-X-K/R"), **(i)** the references cited and discussed in the previous Office Action at pp. 8-10 ¶23 are not relevant to the instant invention, **(j)** the compound of the present invention is directed to binding wild-type NCAM protein and the references cited in the previous Office Action are not relevant, and, **(k)** .

16. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

17. On "**(a)**" and "**(b)**", as written, the claims broadly encompass a genus of compounds with 320 combinations for the general formula "K/R_{0-1}-K/R-X-K/R" leaving 8 open positions to be filled by any one of 20 amino acids. Thus the 320 motifs may be matched with $1.15x10^{18}$ possible peptide combinations using only the 20 naturally occurring amino acids. This does not include "mimics" which include but are not limited to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Thus the claims as written constitute an invitation to experiment. First the skilled artisan must construct the applicable compounds and then screen them to determine which compounds "bind to the NCAM Ig1-Ig2 domains" and "stimulate or

promote neurite outgrowth from NCAM presenting cells/and or proliferation thereof' as required by the claims.

18. On "**(c)**", it is noted that the Examiner has partially withdrawn the instant rejection to include 13 peptides which meet the enablement requirement under 35 U.S.C. §112 ¶1. Thus acknowledging a broader breadth of enabled peptides disclosed in the instant application but the Examiner maintains that it remains an insufficient number of species for such a massive genus of ill-defined compounds to be enabled to the full breadth of the claims.

19. On "**(d)**", it is agreed that the motif "K/R_{0-1}-K/R-X-K/R" is critical for the successful manufacture of a peptide that possesses the claimed function. However, the Examiner maintains the rejection on the grounds that the Specification provides inadequate disclosure to support the claims to the full breath of which they are currently drawn.

20. On the Applicant's comments of inconsistency, it is noted the Examiner may rejoin subject matter previously presented or currently withdrawn from consideration if supported by the Specification and within the scope of what is indicated as meeting the requirements of the statute for purposes of examination (MPEP §800).

21. On "**(e)**", according to the Applicant, Examples 3, 4, 9, and 10 of the Specification constitute an invitation to experiment will lead the skilled artisan is to make and screen a decapeptide library then follow it by functional analysis to establish peptides which possess the desired properties, as well as mutants, variants, and derivatives thereof. This presents a burden of undue experimentation and an invitation to experiment.

22. On "**(f)**", Frei *et al.* (July 1992) "Different Extracellular Domains of the Neural Cell Adhesion Molecule (N-CAM) Are Involved in Different Functions." The Journal of Cell Biology

118(1): 177-192 (**IDS #BC**) teaches that fragments of NCAM differ in their effectiveness in stimulating neurite outgrowth (Table I). Irregardless of the asserted limitation to a maximum of 12 amino acids, the claims as written constitute a massive genus of peptides, as well as variants, derivatives, fragments, and mimics thereof to synthesize and characterize. Thus a skilled artisan is presented with a burden of experimentation to determine which mimics of the claimed SEQ ID NO's are useful for making the invention.

23. On "**(g)**", Applicant is correct, the NCAM isoforms as taught by Doherty *et al.* (March 1995) "The Neural Cell Adhesion Molecule and Synaptic Plasticity." J. Neurobiol. **26**(3): 437-446 cannot be considered "mimics" in view of the limitations of the instant claims. However, the issue raised in the previous Office Action was one of the variety of NCAM isoforms in the rubric of NCAM's claimed. Thus the skilled artisan is confronted with a massive peptide and mimic thereof genus as well as three functionally and structurally distinct isoforms of NCAM upon which to practice the claimed invention. The Specification does not provide guidance as to which peptides and their mimics would be applicable leaving the skilled artisan to determine this through great trial and error.

24. On "**(h)**", to clarify the citation of Rao *et al.* (August 1992) "Identification of a Peptide Sequence Involved in Homophilic Binding in the Neural Cell Adhesion Molecule (NCAM)" The Journal of Cell Biology **118**(4): 937-949 (**IDS #DE**) and Rao *et al.* (4 November 1994) "Mechanism of Homophilic Binding Mediated by the Neural Cell Adhesion Molecule NCAM." The Journal of Biological Chemistry **269**(44): 27540-27548 (**IDS #DF**), both teach that not all peptides and/or their mimics are active. Also, although not teaching the motif claimed, "K/R_{0-1}-K/R-X-K/R", does not disqualify these references from relevance due to lack of enablement as

they are from an analogous art. If said references did teach the motif "K/R_{0-1}-K/R-X-K/R", the Examiner respectfully submits that said references would be used to reject the instant claims under 35 U.S.C. §102 and/or §103. Nevertheless, the skilled artisan cannot predict and must resort to experimentation, in the absence of concrete guidance to establish which members of the giant genus claimed of peptides and their mimics have the activity as claimed.

25. On "**(i)**", in response to applicant's argument that Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517, Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495, Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400, Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250, Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223, Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133, Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427 is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the references discussed in the previous Office Action are drawn to a

larger, more encompassing problem of predicting protein function from its sequence, whether it is a massive protein complex (such a G-protein coupled receptor) or peptides (such as 12-mers). All proteins, large and small, are composed of amino acids, which all share inherent properties and obstacles that must be addressed for the successful practicing of the invention. The Specification as filed does not provide sufficient guidance to practice the invention to the full scope of the claims absent a great undertaking of trial and error experimentation with no guidance in an unpredictable field of endeavor.

26. On "**(j)**", as discussed above, the Specification as filed fails to provide guidance or examples of any compounds that may used to practice the invention other than the following peptides ASKKPKRNIKA (SEQ IN NO: 1), AKKERQRKDTQ (SEQ IN NO: 2), ARALNWGAKPK (SEQ IN NO: 3), AGSAVKLKKKA (SEQ IN NO: 4), ATNKKTGRRRR (SEQ IN NO: 9), ARQKTMKPRRS (SEQ IN NO: 12), ARKTRERKSKD (SEQ IN NO: 14), ASQAKRRRKGPR (SEQ IN NO: 15), AKKEKPNKPND (SEQ IN NO: 17), AEGGKKKKMRA (SEQ IN NO: 19), AKKKEQKQRNA (SEQ IN NO: 20), AKSRKGNSSLM (SEQ IN NO: 21), and ARKSRDMTAIK (SEQ IN NO: 22). An undue burden of experimentation, in a unpredictable field of endeavor, in the absence of guidance and examples is necessary to practice the instant invention with any other peptide or compound.

27. On "**(k)**", as discussed above, even when constraining the instant claims to a peptide, mimic, compound, derivative, fragment, and/or variant which is at most 12 amino acids long and has the motif "K/R_{0-1}-K/R-X-K/R" (leaving 8 open positions to be filled by any one of 20 amino acids), the peptide has a potential of 320 motifs which may be contained in any one of $1.15x10^{18}$ possible peptide combinations. This represents a massive genus of 340 possible motifs and a

grand total of $1.15x10^{18}$ peptides, not counting other non-peptide compounds. The Specification as filed does not provide sufficient guidance to practice the invention to the full scope of the claims as written.

28. The rejection of claims **98-113** and **135-147** under 35 U.S.C. §112 ¶1 is hereby maintained.

Summary

29. Claims 98-113 and 135-147 are hereby rejected.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

31. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
November 21, 2003

Gary L. Kunz
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